Patent Number 4,938,763

Paper No. 14

NOTICE OF REQUEST FOR REEXAMINATION

A request for reexamination of Patent Number 4,938,763 was received on 4-27-93 and has been assigned Reexamination Control Number 90/003037

This notice incorporated by reference into the Patent File all papers entered into the reexamination file. The reexamination file will be included as part of the patent file upon the issuance of the certificate. See, generally, 37 CFR 1.515 (a), 1.520, 1.570.

United States Patent [19]

Dunn et al.

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[54] **BIODEGRADABLE IN-SITU FORMING IMPLANTS AND METHODS OF PRODUCING THE SAME**

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[51] **Int. Cl.**[5] **A61K 9/22**

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[58] **Field of Search** ..... 600/37; 433/180, 201.1, 433/228.1; 604/890.1, 891.1, 27, 48, 49, 54, 93; 424/426, 435; 514/900; 128/156, DIG. 8, DIG. 21, 89 R; 623/11, 16; 606/76, 77

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[57] **ABSTRACT**

A biodegradable polymer is provided for use in providing syringeable, in-situ forming, solid biodegradable implants for animals. The polymer is placed into the animal in liquid form and cures to form the implant in-situ. A thermoplastic system to form said implant comprises the steps of dissolving a non-reactive polymer in biocompatible solvent to form a liquid, placing the liquid within the animal, and allowing the solvent to dissipate to produce the implant. An alternative, thermosetting system comprises mixing together effective amounts of a liquid acrylic ester terminated, biodegradable prepolymer and a curing agent, placing the liquid mixture within an animal and allowing the prepolymer to cure to form the implant. Both systems provide a syringeable, solid biodegradable delivery system by the addition of an effective level of biologically active agent to the liquid before injection into the body.

19 Claims, 2 Drawing Sheets

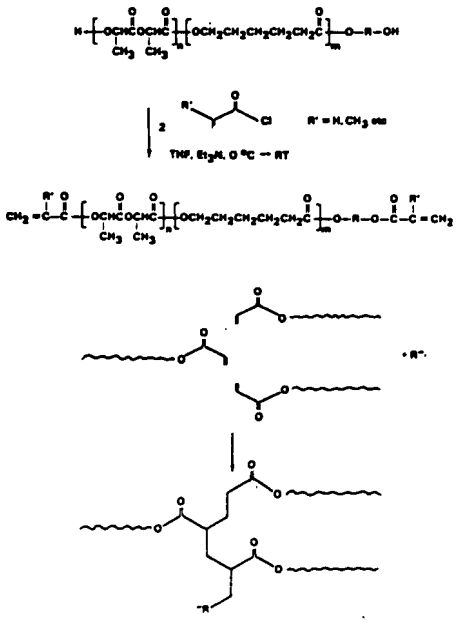
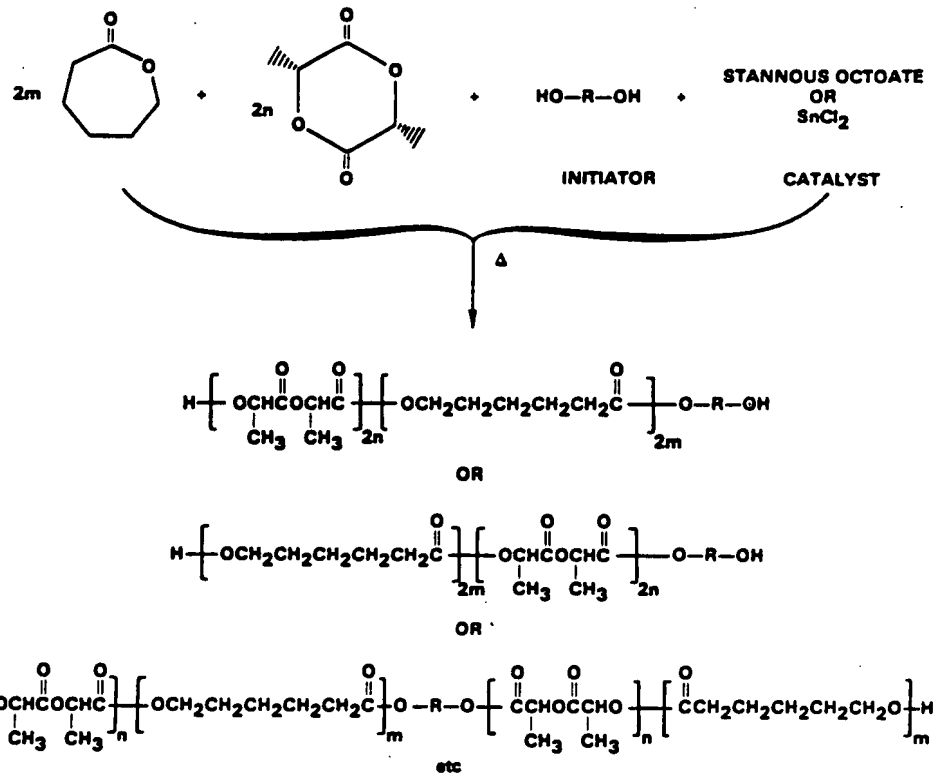


FIG. 2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as muscle or fat, hard tissue such as bone, or a cavity such as the periodontal, oral, vaginal, rectal, nasal, or a pocket such as a periodontal pocket or the cul-de-sac of the eye. For drug-delivery systems, the biologically active agent is added to the polymer solution where it is either dissolved to form a homogeneous solution or dispersed to form a suspension or dispersion of drug within the polymeric solution. When the polymer solution is exposed to body fluids or water, the solvent diffuses away from the polymer-drug mixture and water diffuses into the mixture where it coagulates the polymer thereby trapping or encapsulating the drug within the polymeric matrix as the implant solidifies. The release of the drug then follows the general rules for diffusion or dissolution of a drug from within a polymeric matrix.

Another embodiment of the invention is also provided, namely, a thermosetting system comprising the synthesis of crosslinkable polymers which are biodegradable and which can be formed and cured in-situ. The thermosetting system comprises reactive, liquid, oligomeric polymers which contain no solvents and which cure in place to form solids, usually with the addition of a curing catalyst.

The multifunctional polymers useful in the thermosetting system are first synthesized via copolymerization of either DL-lactide or L-lactide with ϵ-caprolactone using a multifunctional polyol initiator and a catalyst to form polyolterminated prepolymers. The polyol-terminated prepolymers are then converted to acrylic ester-terminated prepolymers, preferably by acylation of the alcohol terminus with acryloyl chloride via a Sohotten-Baumann-like technique, i.e., reaction of acyl halides with alcohols. The acrylic ester-terminated prepolymers may also be synthesized in a number of other ways, including but not limited to, reaction of carboxylic acids (i.e., acrylic or methacrylic acid) with alcohols, reaction of carboxylic acid esters (i.e., methyl acrylate or methyl methacrylate) with alcohols by transesterification, and reaction of isocyanatoalkyl acrylates (i.e.. isocyanatoethyl methacrylate) with alcohols.

The liquid acrylic-terminated prepolymer is cured, preferably by the addition of benzoyl peroxide or azobisisobutyronitrile, to a more solid structure. Thus, for an implant utilizing these crosslinkable polymers, the catalyst is added to the liquid acrylic-terminated prepolymer immediately prior to injection into the body. Once inside the body, the crosslinking reaction will proceed until sufficient molecular weight has been obtained to cause the polymer to solidify. The liquid prepolymer, when injected, will flow into the cavity or space in which it is placed and assume that shape when it solidifies. For drug delivery utilizing this system, biologically active agents are added to the liquid polymer systems in the uncatalyzed state.

In both the thermoplastic and the thermosetting systems, the advantages of liquid application are achieved. For example, the polymer may be injected via syringe and needle into a body while it is in liquid form and then left in-situ to form a solid biodegradable implant structure. The need to form an incision is eliminated, and the implant will assume the shape of its cavity. Furthermore, a drug-delivery vehicle may be provided by adding a biologically active agent to the liquid prior to injection. Once the implant is formed, it will release the agent to the body and then biodegrade. The term "biologically active agent" means a drug or some other substance capable of producing an effect on a body.

It is an object of the present invention, therefore, to provide a method and composition for producing biodegradable polymers.

It is also an object of the present invention to provide such a polymer which may be useful in producing syringeable, in-situ forming, solid biodegradable implants.

It is a further object of the present invention to provide such an implant which can be used in a controlled-release delivery system for biological agents.

It is a further object of the present invention to provide implants having a range of properties from soft and elastomeric to hard and rigid, so as to be usable with both soft and hard tissue.

BRIEF DESCRIPTION OF THE FIGURES AND TABLES

FIG. 1 illustrates the synthesis of acrylate-terminated prepolymers and subsequent crosslinking by free-radical initiators;

FIG. 2 illustrates structures for the random copolymer of ϵ-caprolactone and L-lactide initiated with a diol;

Table 1 is a summary of the bifunctional PLC prepolymers synthesized;

Table 2 is a summary of the acrylic ester terminated prepolymers synthesized; and

Table 3 is a summary of curing studies.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to biodegradable, in-situ forming implants and methods for producing the same. The present invention also relates to a liquid biodegradable polymeric delivery system that can be injected into a body where it forms a solid and releases a biologically active agent at a controlled rate. Two types of biodegradable polymeric systems are described: thermoplastic polymers dissolved in a biocompatible solvent and thermosetting polymers that are liquids without the use of solvents.

A. Thermoplastic System

A thermoplastic system is provided in which a solid, linear-chain, biodegradable polymer is dissolved in a biocompatible solvent to form a liquid, which can then be administered via a syringe and needle. Examples of biodegradable polymers which can be used in this application are polylactides, polyglycolides, polycaprolactones, polyanhydrides, polyamides, polyurethanes, polyesteramides, polyorthoesters, polydioxanones, polyacetals, polyketals, polycarbonates, polyorthocarbonates, polyphosphazenes, polyhydroxybutyrates, polyhydroxyvalerates, polyalkylene oxalates, polyalkylene succinates, poly(malic acid), poly(amino acids), polyvinylpyrrolidone, polyethylene glycol, polyhydroxycellulose, chitin, chitosan, and copolymers, terpolymers, or combinations or mixtures of the above materials. The preferred polymers are those which have a lower degree of crystallization and are more hydrophobic. These polymers and copolymers are more soluble in the biocompatible solvents than the highly crystalline polymers such as polyglycolide and chitin which also have a high degree of hydrogen-bonding. Preferred materials with the desired solubility parameters are the polylactides, polycaprolactones, and copolymers of these with glycolide in which there are more amorphous regions to enhance solubility.

antihistamines, cardioactive agents, non-steroidal anti-inflammatory agents, antiparkinsonian agents, antihypertensive agents, β-adrenergic blocking agents, nutritional agents, and the benzophenanthridine alkaloids. To those skilled in the art, other drugs or biologically active agents that can be released in an aqueous environment can be utilized in the described injectable delivery system. Also, various forms of the drugs or biologically active agents may be used. These include without limitation forms such as uncharged molecules, molecular complexes, salts, ethers, esters, amides, etc., which are biologically activated when injected into the body.

The amount of drug or biologically active agent incorporated into the injectable, in-situ, solid forming implant depends upon the desired release profile, the concentration of drug required for a biological effect, and the length of time that the drug has to be released for treatment. There is no critical upper limit on the amount of drug incorporated into the polymer solution except for that of an acceptable solution or dispersion viscosity for injection through a syringe needle. The lower limit of drug incorporated into the delivery system is dependent simply upon the activity of the drug and the length of time needed for treatment.

In all cases, the solid implant formed within the injectable polymer solution will slowly biodegrade within the body and allow natural tissue to grow and replace the impact as it disappears. Thus, when the material is injected into a soft-tissue defect, it will fill that defect and provide a scaffold for natural collagen tissue to grow. This collagen tissue will gradually replace the biodegradable polymer. With hard tissue such as bone, the biodegradable polymer will support the growth of new bone cells which will also gradually replace the degrading polymer. For drug-delivery systems, the solid implant formed from the injectable system will release the drug contained within its matrix at a controlled rate until the drug is depleted. With certain drugs, the polymer will degrade after the drug has been completely released. With other drugs such as peptides or proteins, the drug will be completely released only after the polymer has degraded to a point where the non-diffusing drug has been exposed to the body fluids.

B. Thermosetting System

The injectable, in-situ forming biodegradable implants can also be produced by crosslinking appropriately functionalized biodegradable polymers. The thermosetting system comprises reactive, liquid, oligomeric polymers which cure in place to form solids, usually with the addition of a curing catalyst. Although any of the biodegradable polymers previously described for the thermoplastic system can be used, the limiting criteria is that low-molecular-weight oligomers of these polymers or copolymers must be liquids and they must have functional groups on the ends of the prepolymer which can be reacted with acryloyl chloride to produce acrylic ester capped prepolymers.

The preferred biodegradable system is that produced from poly(DL-lactide-co-caprolactone), or "DL-PLC". Low-molecular-weight polymers or oligomers produced from these materials are flowable liquids at room temperature. Hydroxy-terminated PLC prepolymers may be synthesized via copolymerization of DL-lactide or L-lactide and ε-caprolactone with a multifunctional polyol initiator and a catalyst. Catalysts useful for the preparation of these prepolymers are preferably basic or neutral ester-interchange (transesterification) catalysts. Metallic esters of carboxylic acids containing up to 18 carbon atoms such as formic, acetic, lauric, stearic, and benzoic are normally used as such catalysts. Stannous octoate and stannous chloride are the preferred catalysts, both for reasons of FDA compliance and performance.

If a bifunctional polyester is desired, a bifunctional chain initiator such as ethylene glycol is employed. A trifunctional initiator such as trimethylolpropane produces a trifunctional polymer, etc. The amount of chain initiator used determines the resultant molecular weight of the polymer or copolymer. At high concentrations of chain initiator, the assumption is made that one bifunctional initiator molecule initiates only one polymer chain. On the other hand, when the concentration of bifunctional initiator is very low, each initiator molecule can initiate two polymer chains. In any case, the polymer chains are terminated by hydroxyl groups, as seen in FIG. 1. In this example, the assumption has been made that only one polymer chain is initiated per bifunctional initiator molecule. This assumption allows the calculation of a theoretical molecular weight for the prepolymers.

A list of the bifunctional PLC prepolymers that were synthesized is given in Table 1. Appropriate amounts of DL-lactide, ε-caprolactone, and ethylene glycol were combined in a flask under nitrogen and then heated in an oil bath at 155° C. to melt and mix the monomers. The copolymerizations were then catalyzed by the addition of 0.03 to 0.05 wt % $SnCl_2$. The reaction was allowed to proceed overnight. The hydroxyl numbers of the prepolymers were determined by standard titration procedure. The Gardner-Holdt viscosities of the liquid prepolymers were also determined using the procedures outlined in ASTM D 1545. The highest molecular-weight prepolymer (MW = 5000) was a solid at room temperature; therefore, its Gardner-Holdt viscosity could not be determined.

The diol prepolymers were converted to acrylic-ester-capped prepolymers via a reaction with acryloyl chloride under Schotten-Baumann-like conditions, as seen in FIG. 2 and summarized in Table 2. Other methods of converting the diol prepolymers to acrylic-ester-capped prepolymers may also be employed.

Both THF and dichloromethane were evaluated as solvents in the acylation reactions. Several problems were encountered when THF was used as the solvent. The triethylamine hydrochloride formed as a by-product in the reaction was so finely divided that it could not be efficiently removed from the reaction mixture by filtration. Triethylamine hydrochloride ($Et_3N.HCl$) has been reported to cause polymerization of acrylic species (U.S. Pat. No. 4,405,798). In several instances, where attempts to remove all of the $Et_3N.HCl$ failed, the acrylic-ester-capped prepolymers gelled prematurely. Thus, to effectively remove all of the $Et_3N.HCl$, it was necessary to extract the prepolymers with water. For reactions carried out in THF, it is preferred that one first evaporate the THF in vacuo, redissolve the oil in CH_2Cl_2, filter out the $Et_3N.HCl$, and then extract the CH_2Cl_2 layer with water. Stable emulsions were sometimes encountered during extraction. The acylations were later carried out in CH_2Cl_2 instead of THF. The filtration of $Et_3N.HCl$ from the reaction mixture was found to be much easier using this solvent, and the organic fraction could be extracted directly with water after filtration.

dure as described in Example 1 showed that the higher drug loadings gave a lower fractional rate of release as normally obtained for matrix delivery systems with diffusional release. The 2%-loaded formulation gave 65% release after 1 day, 75% after 2 days, and 88% after 5 days; the 7%-loaded formulation gave 48% release after 1 day, 52% after 2 days, and 58% after 5 days; and the 14%-loaded formulation gave 38% release after 1 day, 43% after 2 days, and 49% after 5 days.

EXAMPLE 6

Poly(DL-lactide-co-glycolide) was prepared by the ring-opening polymerization of a mixture of DL-lactide and glycolide using lauryl alcohol as the initiator and stannous chloride as the catalyst. The proportions of the two monomers were adjusted so that the final copolymer(DL-PLG) had a 50:50 ratio of the two monomers as determined by nuclear magnetic resonance spectrophotometry. The initiator was also adjusted to give a copolymer with a theoretical molecular weight of 1500 daltons. The copolymer was dissolved in NMP to give a 70% by weight polymer solution. SaCl was added to this solution to give a 2% by weight dispersion of the drug in the polymer solution. The release of drug from this formulation was determined using the same procedure described in Example 1. A much lower release rate was obtained from the copolymer than from the DL-PLA oligomer or DL-PLA 2000 molecular weight materials. After 2 days approximately 7% of the drug was released, 10% after 5 days, 12% after 7 days, and 16% after 14 days.

EXAMPLE 7

SaEt was added to the same solution of DL-PLG in NMP as described in Example 6 to give a 2% by weight solution of the drug. The release of drug from this formulation was determined by the same procedure as described previously. The release rate of SaEt from this formulation was identical to that for SaCl described in Example 6.

EXAMPLE 8

Tetracycline as the free base (TCB) was added to the same solution of DL-PLG in NMP as described in Example 6. The drug dissolved completely in the polymer solution to give a 2.4% by weight solution of the drug. The release of the drug from this formulation was determined by a similar procedure to that described in Example 1 except the receiving fluid was not acidified to a pH of 2.76 and the concentration of TCB was determined by UV absorption at the wavelength appropriate for the drug. The release of TCB from this formulation was more linear and at a much higher rate than that for SaCl or SaEt from the same copolymer. After 1 day approximately 44% of the drug was released, 54% after 2 days, 68% after 5 days, 73% after 6 days, 80% after 7 days, 87% after 9 days, 96% after 12 days, and 100% after 14 days.

EXAMPLE 9

Tetracycline as the hydrochloride salt (TCH) was added to the same solution of DL-PLG in NMP as described in Example 6. The salt form of the drug also dissolved completely in the polymer solution. The release of drug from this formulation was determined as described in Example 8 and found to be similar to that for the free base except for a slightly lower rate. After 1 day approximately 32% of the drug was released, 40% after 2 days, 57% after 5 days, 64% after 6 days, 75% after 7 days, 82% after 9 days, 92% after 12 days, and 100% after 14 days.

EXAMPLE 10

DL-PLA with an inherent viscosity of 0.26 dL/g and a theoretical molecular weight of approximately 10,000 daltons was prepared by the ring-opening polymerization of DL-lactide using lauryl alcohol as the initiator and stannous chloride as the catalyst. The polymer was dissolved in NMP to give a 50% by weight polymer solution. A quantity of the polymer solution (100 μL) was injected subdermally into rabbits, and the tissue reaction was compared to that of a USP negative plastic. The test sites were evaluated for signs of local irritation, in accordance with the Draize method, immediately after injection, at 1 and 6 hours post injection, and once daily thereafter until scheduled sacrifice at 7, 14 or 21 days. The reaction at the test sites was equivalent to that at the control USP negative plastic. The polymer solution (100 μL) was also administered subgingivally into sites created by dental extractions in Beagle dogs. Control sites were flushed with saline solution. The dogs were examined daily for signs of mortality, pharmacotoxic effects, body weights, and local gingival irritation. The animals were sacrificed at 15 and 21 days. No distinct differences were noted between the control and test sites.

EXAMPLE 11

DL-PLA with an inherent viscosity of 0126 dL/g and a molecular weight of about 10,000 was dissolved in NMP to give a 50% by weight polymer solution. SaCl was added to the polymer solution to give a 2.4% by weight dispersion. This material was loaded into a 1-cc disposable syringe fitted with a 23-gauge blunted-end syringe needle, and the material was inserted into the periodontal pocket of a greyhound dog. The material flowed easily out of the narrow syringe tip. The polymer precipitated or coagulated into a film or solid mass when it contacted the saliva and fluid within the pocket. The dog was observed over a time of 2 weeks during which the mass of material remained within the pocket, adhering to tissue surrounding the pocket, and slowly changing color from a light orange to a pale white. The crevicular fluid from the pocket containing the implant was sampled during this 2-week period using Periostrips which are small strips of paper that are placed at the entrance to the periodontal pocket to wick up small quantities of the crevicular fluid within the pocket. The volume of fluid collected is determined using a Periotron which measures the changes in conductance of the paper strip. The Periotron is calibrated before use with a known volume of serum. The paper strip containing the collected fluid is then extracted with a solution of 0.5% by volume of hydrochloric acid in methanol and injected into a liquid chromatograph where the quantity of drug is determined by reference to a known concentration of the same compound. The quantity of SaCl extracted from the paper strip is divided by the quantity of crevicular fluid collected to calculate the concentration of drug in the fluid. With this technique, the concentration of SaCl within the crevicular fluid from the periodontal pocket with the polymeric delivery system was determined to be almost constant during the 2 weeks of observation. The SaCl concentration in the crevicular fluid was 63.2 μg/mL after 3 days, 80.2